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Disease-a-Month

Viral Hepatitis

ROBERT WARD
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Disease-a-Month

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Viral Hepatitis

ROBERT WARD
SAUL KRUGMAN

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ALTHOUGH a number of viruses are known to attack the liver, this discussion is limited to two kinds of viral hepatitis—infectious and serum hepatitis. Both are believed to be caused by viruses despite the fact that no virus has been isolated and characterized in the usual sense, as, for example, in poliomyelitis and influenza; nor has a specific immunologic test been devised for the recognition of either form of hepatitis.

NOTE: Some of the authors' studies at Willowbrook State School, Staten Island, New York, are reviewed here; they were conducted under the sponsorship of the Commission on Viral Infections, Armed Forces Epidemiological Board, and were supported in part by the Office of the Surgeon General, Department of the Army.

The authors are indebted to Dr. Paul H. Hoch, New York State Commissioner of Mental Hygiene, and to Dr. Harold A. Berman, Director, Willowbrook State School, for their cooperation.

Infectious hepatitis is probably an ancient disease. It has long been known under various aliases—*acute catarrhal jaundice, epidemic jaundice, acute yellow atrophy of the liver* and, more recently *IH* and *virus A hepatitis.*

Serum hepatitis (*homologous serum jaundice, SH, virus B hepatitis*) is a man-made disease, artificially transmitted by the injection of virus contained in blood or blood products or carried on contaminated syringes, needles, stilets or other instruments. It has been recognized for about 20 years and appears to be on the rise, the result at least in part of the widespread use of blood and plasma and their derivatives and also of the popularity of injections of all kinds, necessary and unnecessary, some of which may be associated with improper sterilizing technics.

The clinical manifestations of the two types of hepatitis are much the same. The incubation period, however, is a distinguishing feature: it is relatively short in infectious hepatitis (2–8 weeks), and longer in serum hepatitis (2–6 months). The onset of both forms may be either abrupt or insidious, with fever, headache, anorexia, lassitude or irritability, nausea, vomiting and abdominal pain. Fever and other constitutional manifestations usually subside as jaundice appears. Jaundice may be absent, transitory or full-blown and last for several weeks. The liver is enlarged, tender and gives evidence of injury in the abnormal results of function tests and, on microscopic examination, in the widespread destruction of parenchymal cells.

Generally speaking, both forms of hepatitis are milder in children than in adults. The ratio of nonicteric to icteric cases is not known; in adults it appears to be at least 1:1, and in children it may be higher. In young adults the case fatality rate is approximately 1 or 2 per thousand; in older persons, especially in women past the menopause, it is apt to be higher. In adults the disease usually has a protracted course of 6–8 weeks before the patient feels well.

The exact relationship of the viruses causing these two forms of hepatitis is not clear. It has been postulated that serum hepatitis (SH) virus is some sort of *variant* of infectious hepatitis (IH) virus which (*a*) is so poorly equipped immunogenically that insufficient antibodies are formed to eliminate circulating virus in the usual way or (*b*) is transmitted to the fetus in utero, resulting

in infection of the fetus, followed by specific immunologic tolerance; this provides the setting for the offspring to become an asymptomatic lifelong carrier of serum hepatitis virus. These plausible theories unfortunately cannot be tested readily until the agents in question have been adapted to some practical laboratory animal, embryo or tissue culture.

Today both serum hepatitis and infectious hepatitis appear to be on the increase, and, together, they represent the foremost unsolved problem in the field of infectious diseases.

INFECTIOUS HEPATITIS

Infectious hepatitis, caused by a virus or group of viruses, is a systemic disease characterized by constitutional and gastrointestinal signs and symptoms and by evidence of damage to the liver. The disease appears both sporadically and in epidemics. Among civilians, it occurs predominantly in children; epidemics are common in institutions of various kinds, including those for mental defectives, schools, summer camps and the like. During wartime, large outbreaks have been seen in military groups. Today there is evidence that jaundice, the most distinctive manifestation, occurs in the minority of cases.

Etiology

Modern concepts of the etiology and the natural history of viral hepatitis date from the early days of World War II when Voegt (30) reported from Germany the successful transfer of the virus of infectious hepatitis to man by feeding the duodenal contents of a patient ill with hepatitis. British investigators were the first to demonstrate the presence of the virus in the blood (2) and feces (19). Since then, enormous efforts have been made in many laboratories to adapt hepatitis virus to experimental animals, embryonated eggs and tissue cultures. Occasional intimations of success have not been reproducible. A report issued 5 years ago that hepatitis viruses had been propagated in cultured cells (Detroit-6) derived from human beings still lacks confirmation (26). The reported adaptation of hepatitis virus to chick embryo

TABLE 1.—Comparison of Infectious Hepatitis and Serum Hepatitis Viruses and Diseases Caused by Them

Characteristics	Infectious Hepatitis	Serum Hepatitis
Size	Unknown; passes Seitz EK filter	About 26 mμ
Temperature resistance:		
−15 to −20 C. (2 yr., 4 mo.)	Virus remains active	Virus remains active
56 C., ½ hr.	Virus remains active	Virus remains active
60 C., 4 hr.	—	Virus remains active
60 C., 10 hr. (albumin)	—	Virus inactivated
Resistance to ether	Virus remains active	Virus remains active
Resistance to merthiolate 1:2,000	—	Virus remains active
Resistance to chlorine 1 ppm	Virus remains active	—
Coagulation, settling filtration plus chlorine	Virus inactivated	—
Susceptible host	Man	Man
Pathologic changes	Same	
Season	Fall, winter	Any
Age	Children and young adults	Any
Incubation period	2–8 weeks	8–26 weeks
Clinical features	Same	
Secondary cases	+	0
Virus in stools	+	0
Virus in stools in incubation period	+	0
Virus in blood	+	+
Virus in blood in incubation period	+	+
Virus infective by mouth	+	0
Virus infective parenterally	+	+
Homologous immunity	+	±*
Heterologous immunity	0	0
Gamma globulin suppresses jaundice	+	+†

*Inconclusive; evidence indicates it is inferior to that for infectious hepatitis.

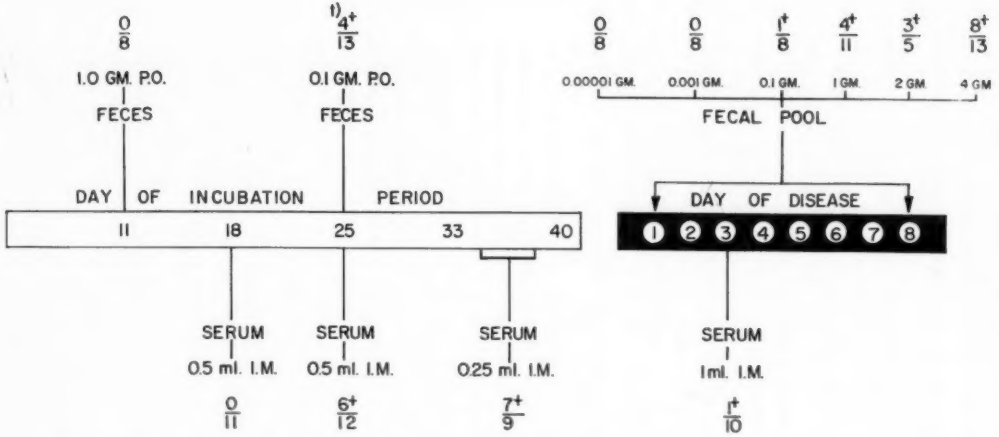
†Effective dose appears to be 10 ml. immediately after transfusion and 10 ml. a month later.

has not been reproduced (14). Today man is still the only known susceptible host. Despite this serious drawback, much has been learned about the natural history of hepatitis from the use of human beings as experimental subjects.

Table 1 lists some of the properties of the two viruses. Although the size of IH virus is unknown, it has been shown to pass through bacteria-retaining filters. This alone provides presumptive evidence that the agent is a virus. It may well be one of the smaller viruses since its close relative, SH virus, has been shown by gradocol-membrane filtration to have a diameter of approximately 26 mμ (20). Infectious hepatitis virus withstands a temperature of 56 C. for 30 minutes. Its activity is preserved for years in the frozen state; the Willowbrook strain was shown to be infective after storage for 2 years and 4 months in an electric freezer at temperatures between —15 and —20 C. The virus is also resistant to ether and appears to be more resistant to chlorine than are many bacteria found in drinking water.

ROUTES OF INFECTIVITY.—Infectious hepatitis is produced in human beings given the virus by mouth and by parenteral routes. Regardless of the portal of entry, the incubation period is the same and virus is excreted in the stools. Since viremia also occurs in infectious hepatitis (see below), it follows that infectious hepatitis, like serum hepatitis, may result from the injection of blood and blood derivatives or from the use of contaminated syringes, needles and other skin- or mucous membrane-piercing instruments. It also follows that since recipients of IH virus by parenteral routes are potential fecal excretors of the virus, secondary cases may result, and precautions should be taken to prevent this. Which virus one is dealing with may be suspected from the incubation period: 2–8 weeks for infectious hepatitis, and 2–6 months for serum hepatitis. In the absence of a history of injection or instrumentation, the possibility of serum hepatitis is reduced.

DISTRIBUTION OF IH VIRUS.—*Virus in stools.*—Infectious hepatitis virus has been demonstrated repeatedly in the stools of patients in the acute stages of the disease. It has been found there in large concentrations; i.e., the equivalent of 0.1 Gm. of feces has been proved to be infective (Fig. 1). The virus is also known to be excreted in the stools *during the incubation period,* 2–3 weeks before the appearance of jaundice (16) (Fig. 1). This suggests



1) 4+/13 HEPATITIS DEVELOPED IN 4 OF 13 SUBJECTS FED THE EQUIVALENT OF 0.1 GM. OF FECES EXCRETED ON THE 25th DAY OF INCUBATION PERIOD.

FIG. 1.—Detection of infectious hepatitis virus (Willowbrook strain) in feces and serum during incubation period and acute stage of illness, in studies of period of infectivity. Virus was detected in stool obtained the 25th day of incubation (2 or 3 weeks before onset of jaundice) and 1st to 8th day of disease. Viremia was detected (1) the 25th day of incubation, (2) 3–7 days before onset of jaundice, and (3) the 3d day of disease.

Stools and serums collected on 11th and 25th days of incubation were from 3 patients; 15 others contributed to serum pool, collected 3–7 days before onset of jaundice. Stool pool no. 1 was prepared from stools in first 8 days after onset of jaundice in 6 naturally infected patients. Serum was obtained from 1 patient the 3d day after onset of jaundice. (Modified from Krugman and Ward, *Infectious Diseases of Children* [2d ed.; St. Louis: C. V. Mosby Company, 1960].)

that people may be dangerous spreaders of infection for an appreciable time before the disease is recognized in them.

How long does virus persist in the stools following the acute stage? Data with which to answer this all-important question are scanty. Early investigators failed to detect virus in the feces of adult patients 3 weeks after disappearance of jaundice and 1 month after onset of illness (8), respectively. (The number of such attempts and the number of volunteers given the test materials were sharply limited.) The excretion of virus in the stools of two infants with chronic hepatitis, 5 and 15 months after onset, respectively, was reported by Capps, Bennett and Stokes (3). Their study was important and should be repeated, since these infants and others like them were apparently the source of an epidemic among the student nurses in the institution. In any event, it is clear that a systematic study is needed to determine the duration of virus excretion in the wake of acute infectious hepatitis.

Viremia.—As already mentioned, IH virus has been detected in the blood. This has been accomplished repeatedly during the acute stages of the disease (2, 8, 24, 25). Virus has also been found in the blood during the incubation period; Francis, Frisch and Quilligan (6) demonstrated viremia in a patient 3 days before the onset of hepatitis. Our investigations with Giles, Jacobs and Bodansky (16) have also demonstrated that viremia occurs during the incubation period; in the first study viremia was demonstrated 3–7 days, and in the second, 2–3 weeks before the emergence of jaundice (Fig. 1). Virus was not shown to be present in a pool of serums collected 3–4 weeks before the onset of jaundice. From epidemiologic evidence, it seems likely that very small amounts of blood or serum are infective; to secure quantitative data concerning this, a titration of virus was performed on a pool of serums collected 3–7 days before the onset of jaundice. The results appear in Table 2. Of nine patients given injections of undiluted serum, six acquired hepatitis, three with and three without jaundice, after incubation periods ranging from 31 to 43 days; of 10 given serum diluted 1:10, six acquired hepatitis, all with jaundice, following longer incubation periods of 45–55 days; of 11 given serum diluted 1:100, one acquired hepatitis without jaundice on the 43d day. The 50%-infectivity dose is estimated at 0.25 ml. of 1:10 dilution. The longer incubation periods with

Ward, *Infectious Diseases of Children* [2d ed.; St. Louis: C. V. Mosby Company, 1960].)

Stools and serums collected on 11th and 25th days of jaundice, and (3) the 3d day of disease.

TABLE 2.—INFECTIOUS HEPATITIS
Titration of Willowbrook Serum Pool No. 2

SERUM DOSE, 0.25 ML. I.M.	NO. OF SUBJECTS	RESULTING CASES OF HEPATITIS		
		With Jaundice	Without Jaundice	Total
Undiluted	9	38, 42, 43*	31, 38, 38*	6
Diluted 1:10	10	45, 49, 49, 49, 55, 55*	—	6
Diluted 1:100	11	—	43*	1

*Number of days of incubation period.

diluted serum and the fact that all six recipients acquired jaundice are remarkable observations, but because of the small numbers involved, they may be the result of chance.

The possible persistence of viremia after recovery from infectious hepatitis has not been thoroughly studied. Murray and his co-workers (23) detected virus in the blood of one person 8 months after recovery, when results of liver function tests were normal. As was the case when virus was looked for in the feces, a limited number of tests failed to demonstrate viremia 1 month after onset of the disease and also 3 weeks after the disappearance of jaundice (8).

Viremia has been demonstrated in a case of inapparent infectious hepatitis in a child (17). This is not surprising, since clinical and epidemiologic evidence of inapparent hepatitis has existed for years, but the demonstration of viremia provides proof. A 6-year-old boy was observed daily for over 2 months following the administration of known icterogenic material. During this period he had no symptoms, no fever, no hepatomegaly, no jaundice, no bilirubinuria and no abnormal deviation of the serum bilirubin, thymol turbidity or cephalin flocculation tests. The sole change detected in this patient was an elevation of the serum glutamic oxalacetic transaminase, which showed a peak value of 250 units at 37 days. Serum drawn then from the patient produced hepatitis in six of eight persons inoculated; hepatitis was associated with typical jaundice in three and without jaundice in three, after incubation periods ranging from 33 to 47 days. Although the stools of this child with proved viremia and inapparent hepatitis were not tested for virus, it would be surprising not to find it in view of the positive results obtained from stools in the incubation

period and because of the observations of others (3). These findings suggest that the most efficient and dangerous spreaders of IH virus are persons with inapparent disease and persons in the incubation period.

Pathology

The principal pathologic changes are found in the liver, which has been examined not only post mortem but also by means of biopsies at various stages of the disease. The characteristic finding during the acute state is widespread destruction of parenchymal cells. In later stages, biopsies usually show complete regeneration of the liver cells at the end of 2 or 3 months. The pathologic findings in serum hepatitis are identical with those of infectious hepatitis.

In *fulminating hepatitis,* fatal within 10 days, the size of the liver may be reduced and its color mottled or yellow (acute yellow atrophy). The cells are completely wiped out and there is no indication of regeneration. Heavy infiltration by cells, mainly mononuclear, is seen within and outside the lobule. Numerous macrophages and erythrocytes appear in the lobular remnants. The liver resembles a spongy framework filled with inflammatory cells and blood.

In *subacute hepatitis,* with fatal outcome in 3–8 weeks, the liver may be reduced in size or may be larger than normal. It is often grossly deformed. Yellow-green nodules are seen around red, depressed areas. The cut surface is often granular and there is irregular and patchy destruction of the parenchyma. Nodular regeneration is evident.

Other changes seen at autopsy include hemorrhage and inflammation in the walls of the stomach and intestine, generalized lymph node enlargement and splenomegaly.

Clinical Manifestations

The *incubation period* of infectious hepatitis ranges from 2 to 8 weeks. This is in contrast to the longer incubation period (8–26 weeks) of serum hepatitis and occasionally may help to distinguish

one from the other. The incubation period in infectious hepatitis does not seem to be influenced by the source of infecting virus (stool or serum), the dose of virus or the portal of entry. The determining factor appears to be the strain of virus; some strains take 2–3 weeks to produce disease, and others take longer. We found the Willowbrook strain to have a mean average incubation period of 45 days before the onset of jaundice (range 35–56, median 44 days).

The course of the disease is often separated into two phases, preicteric and icteric, although occasionally jaundice may be the presenting complaint. The onset may be sudden or gradual, with fever, loss of appetite, headache, irritability or lassitude, and nausea, vomiting and abdominal discomfort. Older children and adults may complain of pain in the right upper quadrant or epigastrium. In some patients the liver is enlarged and tender at this stage. The spleen may be palpable and the posterior cervical lymph nodes may be enlarged. In adults and older children, the temperature ranges between 100 and 104 F. and usually lasts 2–5 days (Fig. 2). Chills or chilly sensations may be associated with fever. With other systemic symptoms, the fever usually subsides at about the time jaundice appears. Fever is often absent or transitory in young children. In young children the transition to the icteric phase is frequently accompanied by the disappearance of symptoms. The patient's appetite returns and he often feels well when the jaundice is at its height. In older children and adults, on the other hand, the emergence of jaundice may be associated with an exacerbation of some of the original symptoms, e.g., anorexia, nausea, vomiting and abdominal pain. Bradycardia, pruritus and mental depression, all common symptoms in adults, are uncommon in children.

The liver is enlarged and tender. The spleen is felt in about one quarter of the cases. The stools may be clay-colored, but this is not a constant finding. The icteric phase lasts from several days to as long as a month, the average duration being 8–11 days in children in contrast to 3–4 weeks in adults. As jaundice fades, the patient's appetite and sense of well-being return. Convalescence is usually rapid and uneventful. Although adults may suffer weight loss ranging from 5 to 25 lb., we have not observed this in children.

In small infants and children under 3 years, there is evidence

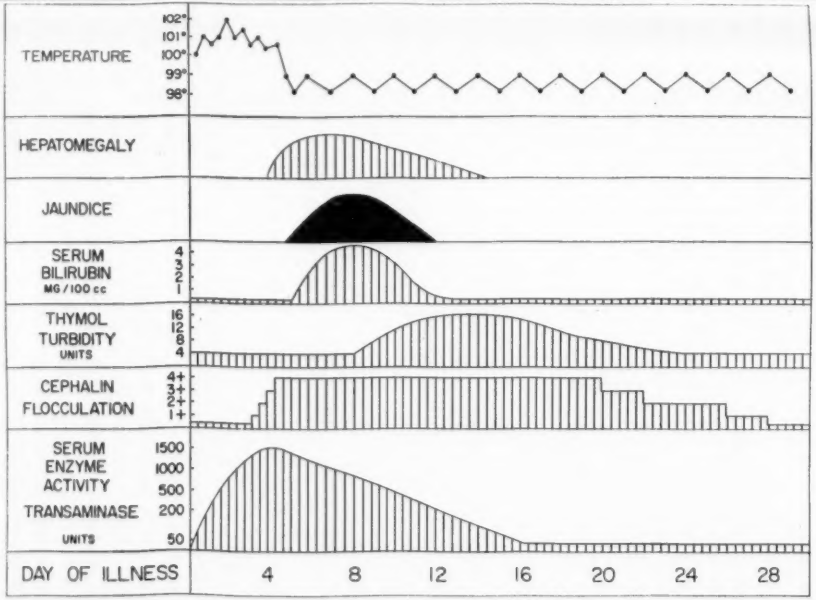


FIG. 2.—Diagram of clinical course of infectious hepatitis; correlation of liver function tests with clinical manifestations. (Figs. 2 and 3 from Krugman and Ward, *Infectious Diseases of Children* [2d ed.; St. Louis: C. V. Mosby Company, 1960].)

that hepatitis may be predominantly nonicteric. Capps and his co-workers (3) found only one with overt jaundice among 36 infants with endemic hepatitis studied in an orphanage; the symptoms in the rest were nonspecific, such as failure to gain weight, loose and light-colored stools, fever, anorexia, respiratory symptoms, lassitude, abdominal distention and vomiting. The probability that some of these patients did indeed have nonicteric hepatitis is reinforced by the detection of IH virus in the stools of two of them; this was accomplished by feeding a fecal suspension to adult volunteers in whom hepatitis with jaundice developed after 22 and 26 days, respectively.

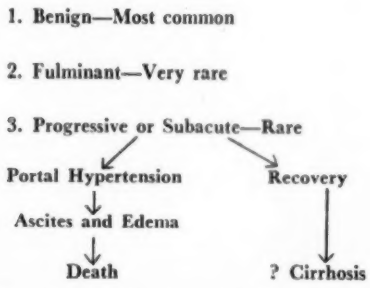


FIG. 3.—Possible courses of viral hepatitis.

One of us (S.K.) studied 29 children and adults intensively for 6 months after their admission to an institution where infectious hepatitis was endemic. Thirteen of the 29 patients acquired hepatitis, five with and eight without jaundice, an 8:5 ratio of nonicteric to icteric cases (18).

The course of infectious hepatitis is usually benign and uncomplicated (Fig. 3). In rare instances, usually in adult patients, there may be a fulminating course characterized by sudden onset of mental confusion, emotional instability, restlessness, coma and bleeding manifestations. Sometimes hepatitis takes a progressive or subacute course leading either (*a*) to recovery or eventually to cirrhosis or (*b*) to portal hypertension with ascites and edema, usually ending fatally within a year.

LABORATORY FINDINGS.—There is neither a specific laboratory test for hepatitis virus nor one for man's response to infection with this agent. There is available, however, a battery of laboratory tests which, in most cases, help to establish the diagnosis. During the preicteric phase, leukopenia is a characteristic finding, and many large atypical lymphocytes like those seen in infectious mononucleosis may be observed toward the end of the preicteric phase. Bilirubinuria, a most important clue, often precedes the onset of jaundice by several days. Early, often in the preicteric phase, reactions to the cephalin flocculation and thymol turbidity tests become positive. Other liver function tests, including that of sulfobromophthalein retention, may also become abnormal. The rise in serum bilirubin usually keeps pace with the jaundice. The Van den Bergh reaction shows an increase in the direct-reacting fraction. Certain enzymes have also been discovered in increased concentration in the serum of patients with hepatitis. These include the transaminases (glutamic oxalacetic and glutamic pyruvic), phosphohexose-isomerase, lactic acid dehydrogenase and alkaline phosphatase. An increase in the concentration of one or another of these enzymes may precede the emergence of jaundice or other signs of liver dysfunction by as long as a week. The increase in serum glutamic oxalacetic transaminase proved to be, in our experience, the most useful single criterion in the diagnosis of infectious hepatitis.

As jaundice disappears, an increase in urine urobilinogen often takes place. False positive serologic tests for syphilis (precipitin and complement fixation) may be observed. A skin test, using as antigen material from embryonated hen's egg, was reported several years ago but has not been reproduced (13). More recently Havens (12) has demonstrated hemagglutinins for 1-day-old-chick erythrocytes in the serum of patients in the acute stages of viral hepatitis. Positive results were also obtained in a small percentage of normal persons and of patients with chronic hepatic disease and other acute and chronic diseases; no hemagglutinins were found, however, in the serum of 23 patients with obstructive jaundice. McCollum and his associates (21) have recently reported essentially similar results.

The relationship of certain tests of liver function to the clinical course of hepatitis in a child is shown in Figures 2 and 4.

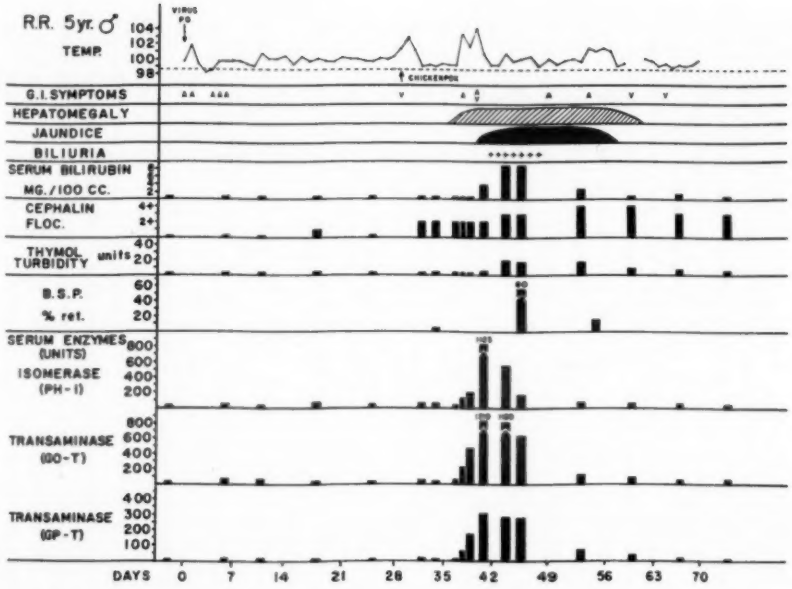


FIG. 4.—Course of hepatitis after feeding Willowbrook pool no. 1 (unheated). Jaundice was detected the 41st day; hepatomegaly and abnormal liver function tests, the 39th day. Illness was mild and patient gained 3 lb. during course. Gastrointestinal symptoms included anorexia (*A*) and vomiting (*V*). (From Ward *et al.* [38].)

Diagnosis and Differential Diagnosis

Since there is neither a specific virologic nor an immunologic test for viral hepatitis, the diagnosis must be made on clinical and epidemiologic grounds with the help of the laboratory tests described above. The index of suspicion will be high if there is an outbreak in the community. During the preicteric phase, or in anicteric hepatitis, the diagnosis is especially difficult. Bilirubinuria, enlargement and tenderness of the liver, leukopenia with relative lymphocytosis, positive results of cephalin flocculation and thymol turbidity tests, abnormal retention of sulfobromophthalein and elevated serum transaminase all point to hepatitis.

Before jaundice appears, the following diseases should be considered in the differential diagnosis: *infectious mononucleosis, acute appendicitis, shigellosis, salmonellosis, influenza* and, in certain parts of the world, *malaria, dengue* and *sandfly fever*. The diagnosis of these infections may be confirmed by the detection of specific causative agents, by serologic tests or by the subsequent course of disease.

After jaundice appears, the diseases usually confused with infectious hepatitis are *serum hepatitis; hemolytic jaundice,* congenital or acquired; *obstructive jaundice,* caused by blockage of the bile ducts by stone, tumor or, in infants, congenital atresia; *hepatocellular jaundice,* resulting from chemical poisons, cirrhosis (e.g., with galactosemia) or tumor of the liver (primary or metastatic); *spirochetal jaundice* (Weil's disease), *yellow fever,* and *acute cholangitis; jaundice accompanying certain other infections,* e.g., sepsis, infectious mononucleosis, brucellosis, amebiasis, malaria and, especially in infants, cytomegalic inclusion disease, generalized herpes simplex, syphilis and toxoplasmosis.

Serum hepatitis.—Serum hepatitis can occasionally be distinguished from infectious hepatitis by the history of a long incubation period (2–6 months) following blood transfusion or the injection of a blood derivative. It should be stressed that not all jaundice which follows blood transfusions, etc., is serum hepatitis; infectious hepatitis may also be transmitted by parenteral injection; and when the incubation period is short (2–8 weeks), one is presumably dealing with infectious hepatitis.

Hemolytic jaundice.—Hemolytic jaundice should be distin-

pool no. 1 (unheated). Jaundice was detected the 41st day; hepatomegaly and abnormal liver function tests, the 39th day. Illness was mild and patient gained 3 lb. during course. Gastrointestinal symptoms included anorexia (*A*) and vomiting (*V*). (*From Ward et al.* [38].)

guished from obstructive jaundice by the history, the presence of anemia, the indirect Van den Bergh reaction, the lack of bile in the urine, the presence of urobilin in the stools and a positive Coombs test.

EXTRAHEPATIC OBSTRUCTIVE JAUNDICE.—In infancy, congenital atresia of the bile ducts, either extra- or intrahepatic, may present difficulties early. The diagnosis should become clear in the course of 2–2½ months as the jaundice deepens progressively and the stools remain acholic. Serum transaminase values appear to be lower than those usually found in infectious hepatitis; results of cephalin flocculation and thymol turbidity tests are usually normal. Other causes of extrahepatic obstructive jaundice such as stones and tumors are rare in children.

HEPATOCELLULAR JAUNDICE.—Hepatocellular jaundice or parenchymal jaundice caused by chemical poisons is usually difficult to recognize in the absence of a history of the use of toxic materials. The history is also important in the diagnosis of cirrhosis or neoplasm. Parenchymal liver cell disease may be caused by such drugs as gold, iproniazid pyrazinoic acid amide and probenecid. Jaundice characterized by cholangitis with biliary stasis may be the result of therapy with chlorpromazine, arsphenamine and methyltestosterone. A story of drug ingestion may furnish an important clue in the differential diagnosis of jaundice.

JAUNDICE ASSOCIATED WITH INFECTIONS.—In this category, the diagnosis is established by detecting the specific causative agent or by a specific serologic test.

COMPLICATIONS

Complications are uncommon, especially in children. A small proportion of patients may have a relapse or prolongation of abnormal liver function, which may or may not be associated with frank manifestations of illness. Posthepatitis cirrhosis may develop in a few of these patients. The ultimate prognosis is poor. Chronic hepatitis is apt to develop in women past the menopause; this is characterized by remissions and exacerbations of jaundice with edema, ascites and hemorrhagic manifestations. The mortality in this group has been reported to be as high as 50%.

Pneumonia and, rarely, aseptic meningitis or encephalopathy may develop in adult patients.

Prognosis

As is the case in most other viral infections, it is better to have infectious hepatitis in childhood than in adult life. The chance for complete recovery is excellent, and it ranks as one of the mildest of childhood infections. In young men in the armed forces the case fatality rate is 1–2 per thousand; in older persons, especially in women past the menopause, it is higher.

The sudden appearance of mental confusion, emotional instability, restlessness, coma and hemorrhagic phenomena are ominous signs. With these manifestations a fulminating course usually proceeds to a fatal outcome within 10 days. Relapse is seen in from less than 1% to about 20% of adult cases. In a small proportion of patients, resolution and repair of the hepatic damage are incomplete; the usual course in them is chronic hepatitis or cirrhosis, and the ultimate prognosis is poor.

Epidemiology

Geographic distribution.—Infectious hepatitis is found all over the world. As with poliomyelitis, hepatitis in epidemic form has been seen in the Scandinavian countries, Iceland, England, Germany, Switzerland, the Balkan countries, the United States and Japan. An explosive water-borne epidemic involving about 29,000 people with jaundice struck Delhi, India, in the winter of 1955-56 (15). It is endemic in other parts of the world, such as the Mediterranean basin and other semitropical and tropical areas, where its presence is often unsuspected and may be revealed during military campaigns by the presence of susceptible troops from other lands.

Age distribution.—Although the highest incidence in civilian populations is in children under 15 years of age, this is often not appreciated because the cases in children are apt to be so mild as to be unrecognized. The adult population, which is relatively immune, provides only a few overt cases. In this way a high incidence of hepatitis within a community may be overlooked. In a

smoldering endemic situation in an institution for mental defectives, approximately three quarters of the cases occurred in those under 20. The ratio of nonicteric to icteric hepatitis was about 2:1. The mildness of the disease in infants and young children makes them dangerous transmitters of infection. As mentioned earlier in a different context, Capps and his co-workers (3) described an epidemic of infectious hepatitis with jaundice in a high proportion of new student nurses caring for infants under 3 years in an orphanage. Hepatitis, for the most part unrecognized, was shown* to be endemic in the infants; accordingly, they were the reservoir of infection for the nurses.

SEX DISTRIBUTION.—Generally speaking, both sexes appear to be equally susceptible to infection. The incidence, however, has been reported to be higher in girls soon after menarche. In women past the menopause there is a higher morbidity for chronic hepatitis and a higher mortality than in men. The incidence is reported to be slightly higher for women than for men among parents of the child-bearing age. This difference has been thought to be the result of the usually more intimate contact of mothers than of fathers with their small children.

SEASONAL DISTRIBUTION.—Infectious hepatitis occurs throughout the year, but in many areas there is a seasonal concentration of cases. In the United States the incidence consistently drops in summer, rises in the late fall, reaches a peak in the winter and drops off in the late spring. In Scandinavian countries the peak is reached in the fall or early winter.

TRANSMISSION.—There is a great deal of evidence that intestinal-oral pathways are the mode of spread of infectious hepatitis. The evidence is derived from both experimental and epidemiologic investigations. The virus of infectious hepatitis is excreted in the feces of both naturally and artificially infected human beings. The disease has been produced experimentally in volunteers by feeding material containing the virus. Outbreaks of hepatitis have occurred repeatedly in association with poor sanitation in military installations. Institutions for mental defectives are famous loci for endemic hepatitis, as well as for salmonellosis and shigellosis; in

*Virus was detected in the stools of two infants by means of transmission of the infection to adult volunteers.

all probability this is the result of the excretory habits of the patients and the impossibility of maintaining proper sanitation. Although explosive water-borne, milk-borne and food-borne epidemics have been described, the most common method of spread is, in all likelihood, through intimate human association. In this regard, it should be emphasized that the pathways in person-to-person contact include the intestinal-oral circuit as well as the "respiratory" or "droplet" or mouth-to-mouth routes. The number of tests for virus on material from the respiratory tract is few, and there is little support of any kind for a respiratory type of spread. The virus of infectious hepatitis, as mentioned earlier, may also be found in the blood, and consequently the disease may be transmitted, as is serum hepatitis, during blood or plasma transfusions or the use of other blood products or by contaminated needles, syringes, stilets and other cutting instruments.

Immunity

There is some evidence that an attack of infectious hepatitis generally provides protection against a second attack. That this immunity may not be as complete as that conferred by measles, for example, is suggested by a previous history of jaundice in 2–5% of patients. This kind of evidence is unreliable, however, because the previous episode of jaundice may have been caused by some other agent, such as SH virus; it is well established that there is no cross-immunity between infectious and serum hepatitis. In a mental institution in which about 525 cases of hepatitis with jaundice were seen in 6 years, second attacks of hepatitis (with jaundice) were observed in 21, or 4%. In one patient, furthermore, two attacks of hepatitis with jaundice were induced experimentally 3 months apart by feeding aliquots of the same virus suspension (31). Complete immunity, on the other hand, has been shown in adult volunteers convalescent from experimental infectious hepatitis and challenged later with homologous virus (9). Evidence of partial cross-immunity was similarly demonstrated for two strains of IH virus.

To explain second attacks of the disease, the existence of multiple immunologically separate and distinct types of IH virus has been postulated. There is ample precedence for this in the family

of enteroviruses, not to mention myxoviruses, adenoviruses and so forth. Since the question cannot be studied systematically without a practical laboratory test, evidence for or against the hypothesis is hard to obtain. There are several other possible explanations for second attacks: (1) Hepatitis virus may become latent following the primary infection, to be stimulated later into activity by unknown factors similar, perhaps, to those acting on herpes simplex. (2) The second attack may be the result of a dose of homologous virus so large as to overwhelm the host's resistance. (3) There may be deficient immune mechanisms in persons subjected to second attacks. Supportive evidence for any of these possibilities is lacking.

Treatment

There is no specific treatment for viral hepatitis. *Bed rest* and *adequate diet* are the mainstays of symptomatic therapy. As a rule, the disease in children is so mild that confinement to bed is difficult to enforce after the acute stage; the child's return to activity is guided best by his own inclinations. For adult patients, the duration of bed rest is debatable. During World War II the experience with combat-weary troops suggested that early return to active duty was apt to be followed by relapse. Studies carried out subsequently in peace-time with occupation troops who, at the onset of hepatitis were in good physical condition, failed to show a relationship between length of bed rest and incidence of relapse or prolongation of the convalescent period (4).

It has been shown that patients who are permitted the freedom of the room or ward, except for a postprandial rest period of 1 hour, do well and are ready and able to go back to work at the end of the illness. This regimen is appropriate for healthy young and vigorous middle-aged adults. A more conservative program is desirable for older patients and especially for those debilitated by other diseases regardless of age. Several tests of liver function are useful as a guide to the restoration of activity of a patient who is free from symptoms; these include: (1) serum transaminase, less than 40 units; (2) serum bilirubin, level below 1.5 mg. per 100 ml.; (3) sulfobromophthalein retention, less than 10% in 45 minutes.

The *diet* may often be regulated by the patient's appetite. In the presence of anorexia, he should be encouraged to take liquids such as broth and fruit juices. With the return of appetite, a normal diet is recommended. This should be adequate in calories, palatable and properly balanced. A moderate amount of fat is not contraindicated; in fact, milk, cream, butter and eggs should be included early to counteract the loss of weight and to shorten the convalescent period. All the vitamins, especially those of the B complex, are recommended to supplement the regular diet.

In the usual uncomplicated case of hepatitis there is no indication for use of either ACTH or cortisone. We have had no occasion to give them to children with hepatitis. The administration of cortisone to adults with severe cases has been reported to have beneficial results. Steroids may be indicated for patients with fulminating hepatitis and for those in hepatic coma. It is also recommended that such patients in acute hepatic failure be given daily intravenous injections of 1–2 liters of 10% dextrose solution and 25 Gm. of salt-poor albumin.

Control Measures

Procedures aimed at blocking intestinal-oral pathways should be carried out, as they are in other excremental infections, in an attempt to control the spread of hepatitis. These measures should include conscientious hand-washing after evacuation of the bowels and before meals; proper cleansing and sterilization of food utensils (boiling or autoclaving for 30 minutes); exclusion of food-handlers who are contacts and potentially infected; fly suppression, and other measures to prevent fecal contamination of food, milk and water supplies. Present evidence indicates that the customary methods of chlorinating water are not reliable for destroying hepatitis virus. There is no practical and reliable method for the detection of nonicteric cases and carriers, although an elevated serum glutamic oxalacetic transaminase level may be helpful (see section on Serum Hepatitis—Control Measures). The duration of virus excretion in the stools and of viremia after the acute stage of illness is unknown. Patients should be considered potentially infectious for at least a week after the onset of illness. Patients should never at any time thereafter serve as blood donors,

and particular attention should be directed to the scrupulous cleansing and heat sterilization of all needles, syringes and other instruments used on them.

The results of recent investigations, which show the presence of virus in the feces and blood during the incubation period of infectious hepatitis, are summarized in Figure 1. These observations bear on the difficult problem of attempting to control the spread of the disease. The task is further aggravated by the large number of persons with nonicteric and unrecognized cases capable of disseminating infection.

GAMMA GLOBULIN.—There is ample evidence that gamma globulin prepared from pools of plasma from normal adults offers a measure of passive protection if given during the incubation period up to 6 days before onset of illness. We believe that it is advisable to give a dose of 0.06 ml. per pound of body weight by the intramuscular route (17); others have reported protection with smaller amounts (28). Passive protection apparently lasts from 6 to 8 weeks. Stokes and his co-workers (28) were the first to call attention to the prolonged protection following injection of gamma globulin in persons exposed in institutional epidemics. Those who received gamma globulin were apparently protected for as long as 9 months; uninoculated controls in the same buildings continued to come down with hepatitis. These authors postulated the acquisition of subclinical infection by the groups given gamma globulin, resulting in active immunity superimposed on passive immunity or, as they termed it, "passive-active" immunity. Our observations have tended to confirm the validity of this concept (17, 31).

From the practical point of view, however, it should be emphasized that the combination of passive and active immunity was acquired in institutions where the type of exposure was heavy and repetitive; other types of exposure, such as occurs in families, may be different, e.g., neither heavy nor repetitive. In the latter instance, the administration of gamma globulin to contacts cannot be relied on to provide "passive-active" immunity.

Recent studies (17) support long-held epidemiologic and clinical impressions that gamma globulin does not always prevent infection. Under the conditions described, gamma globulin appeared to suppress jaundice and to modify the disease so as to

make its clinical recognition more difficult. This may have its good and bad aspects. From the standpoint of the individual, if it can be shown that "modified hepatitis," or nonicteric hepatitis, is as benign as, for example, modified measles and never progresses to chronic hepatitis, cirrhosis or liver failure, this method of immunization against infectious hepatitis should be developed and recommended. From the standpoint of the community and public health, on the other hand, it should be emphasized that the suppression of jaundice by gamma globulin may give a false sense of security in that the so-called "protected" or nonicteric, nevertheless infected, individual will have the opportunity to spread the infection to others more efficiently than the patient with overt jaundice.

SERUM HEPATITIS

Serum hepatitis is indistinguishable from infectious hepatitis on the basis of most of its clinical and pathologic features. It is an artificial, man-made disease caused by the injection of serum hepatitis virus (or viruses) contained in blood or blood products or in contaminated syringes, needles, stilets and other instruments that pierce the skin or mucous membranes. It is characterized by a long incubation period and by the absence of secondary contact cases, both features standing in contrast to infectious hepatitis.

Etiology

The properties of the causative agent, serum hepatitis virus (SH virus or virus B), indicate that it is a close relative of infectious hepatitis virus (IH virus or virus A). A comparison of their characteristics is given in Table 1. Since, as is also true for IH virus, man is the only known susceptible host of SH virus, studies of both agents have been severely handicapped by the lack of an experimental test object. Some of the differences apparent today may vanish as new technics are discovered and as knowledge increases. It seems justified at present to think of them as closely related agents with certain distinguishing features pertaining to incubation period, distribution of virus, portals of entry and exit, secondary cases, epidemiology and, perhaps, immunity.

McCollum (20) measured the SH virus by collodion-membrane filtration and found it to be about 26 mμ. Like IH virus, it is resistant in its capacity to survive various physical and chemical agents. In serum albumin it withstands a temperature of 60 C. for 4 hours but succumbs after 10 hours. It survives in the frozen state for years and in the dried state at room temperature for at least a year. It survives in serum containing either Merthiolate in a concentration of 1:2,000 or tricresol 1:500. Serum hepatitis virus is inactivated in serum exposed to ultraviolet light under certain conditions; since it also has been shown to survive exposure to ultraviolet light under other conditions, ultraviolet light has not yet proved to be a reliable or practical agent of sterilization.

Viremia occurs in serum hepatitis not only during the acute phase of the disease but also during the long incubation period. Virus has been detected in the blood 87 days before onset of disease. Furthermore, persons have been shown to carry SH virus in the blood for years without evidence of hepatic dysfunction. As mentioned earlier, viremia also occurs in infectious hepatitis, so that both forms of hepatitis can be transmitted in the same way; a difference already described is that IH virus is known to be excreted in the feces of persons given parenteral injections, an added danger in infectious hepatitis not present in the transmission of serum hepatitis. Although the number of tests is small, serum hepatitis has not been produced by feeding volunteers with serum known to contain virus, nor has SH virus been detected in the stools. Secondary cases probably do not occur as a result of contact with patients ill with serum hepatitis, another feature which distinguishes it from infectious hepatitis.

Clinical Manifestations

With few exceptions, the clinical manifestations of serum hepatitis are indistinguishable from those of infectious hepatitis. The exceptions are the incubation period, and possibly the mode of onset and severity in young infants and debilitated patients. The incubation period of serum hepatitis is relatively long, ranging from about 2 to 6 months; the incubation period of infectious hepatitis is shorter, varying from about 2 to 8 weeks. The onset of serum hepatitis is reported to be often insidious and afebrile; the

onset of infectious hepatitis, on the other hand, is apt to be abrupt and febrile. These reported differences in the manner of onset seem to us to be inconstant and not to be relied on to differentiate one type of hepatitis from the other. Nonicteric hepatitis occurs in serum hepatitis as it does in infectious hepatitis. There is suggestive evidence that serum hepatitis may be more severe than infectious hepatitis, especially in young infants (22) and in debilitated patients.

The pathologic changes, complications, diagnosis and treatment are the same as those of infectious hepatitis, described earlier.

Epidemiology

Geographic distribution.—Serum hepatitis probably occurs throughout the world in places where blood transfusions, various blood products and parenteral injections of other substances are given. The increased incidence of serum hepatitis during the past two decades is undoubtedly related to (1) the increasing popularity of the aforementioned procedures, (2) the high incidence of the carrier state (estimated at 2–3% of the adult U.S. population (27) and to its long-term persistence (29), (3) the fact that a dose as small as 0.01 ml. of serum may be infective, and (4) the toughness of the virus in resisting various physicochemical agents. Serum hepatitis has been reported from the United States, England, Sweden, Russia and the Middle East.

Season.—No seasonal concentration of cases of serum hepatitis has been observed; this is probably related to the custom of giving blood transfusions and various other parenteral injections at a fairly uniform rate throughout the year.

Age and sex.—Age and sex do not appear to affect susceptibility to serum hepatitis. Although the disease is said to be milder in children, severe cases in infants with high mortality have been reported (22).

Transmission.—Serum hepatitis is transmitted to susceptible persons during blood or plasma transfusions and injections of convalescent serum and serum containing other beneficial substances, fibrin foam, thrombin or vaccines containing human serum. Many cases of serum hepatitis in World War II resulted from the use of certain lots of yellow fever vaccine containing infective human

serum. Epidemics have been traced to diabetic and antisyphilitic clinics where inadequately sterilized needles and syringes were used. It is possible that both serum hepatitis and infectious hepatitis can be transmitted perhaps simultaneously to the same individual. Wewalka (32), cited by Havens (10), described sizable outbreaks in a clinic for antisyphilitic therapy; there were two peaks, the first appearing 4–8 weeks (IH?) after the start of injections, and the second peak appearing 16–20 weeks (SH?) after the start of therapy. Moreover, in certain patients the onset of hepatitis occurred after a short (22 days) or somewhat longer (54 days) incubation period; these episodes were followed by recovery and subsequently by a second attack after a long incubation period (2–5 months after start of therapy). This situation, with at least two immunologically distinct agents being transmitted perhaps simultaneously, points up the hazards in clinics where parenteral injections are given with insufficiently sterilized needles and syringes.

Outbreaks have also been described in drug addicts using the same unsterilized equipment. There is evidence that withdrawal of blood by venipuncture or by stilet puncture of the skin for blood counts, and even tattooing, may be responsible for infection.

Immunity

The lack of practicable methods to measure immunity in serum hepatitis is responsible for the enormous gaps in our knowledge of this subject. There is scanty information concerning the immune response which follows infection with SH virus. Even the limited studies in human volunteers have yielded discordant results: Neefe and his associates (24) demonstrated partial resistance to reinoculation with homologous strains of SH virus at intervals up to about 1 year following recovery from the first attack; Murray and co-workers (23) also showed homologous immunity in volunteers. In addition, the fact that a large proportion of persons inoculated with SH virus, either as volunteers or as patients receiving blood or plasma containing the agent, failed to come down with hepatitis suggests the presence of immunity. In a conflicting report, Drake and his co-workers (5) failed to prevent serum hepatitis in volunteers inoculated simultaneously

with SH virus and with gamma globulin derived from persons convalescent 3 months to 3 years from serum hepatitis. On the other hand, the possibility that gamma globulin may contain antibody to SH virus is supported by the findings of Grossman, Stewart and Stokes (7). They injected two doses of gamma globulin (10 ml. on admission and 10 ml. a month later) in 384 battle casualties who had received blood or plasma and observed close to a 7-fold reduction in the incidence of hepatitis with jaundice in those given gamma globulin as compared with controls. Since the onset of hepatitis in 84% occurred between 8 and 17 weeks after injury (and transfusion), it seems likely that most of the cases represent serum hepatitis. Unpublished studies by Mirick and others tend to confirm these results.

One aspect of immunity in viral hepatitis seems to have been clearly established, i.e., lack of cross-immunity between serum hepatitis and infectious hepatitis. Persons who have had an attack of infectious hepatitis, either naturally acquired or experimentally induced, are susceptible to serum hepatitis; the converse is also true. Indeed, there is suggestive evidence that troops who had had serum hepatitis (resulting from contaminated yellow fever vaccine) were more susceptible to infectious hepatitis (11).

Control Measures

The transmission of serum hepatitis revolves around the presence of healthy carriers of SH virus, with an incidence in the general population estimated to be 2–3%. The lack of laboratory tools for the demonstration of virus or antibody is a severe handicap in efforts to control the disease. A recent report (1) suggests that at least a proportion of carriers may be recognized by elevated serum glutamic oxalacetic transaminase (SGO-T) activity in the prospective donor's blood; with an SGO-T activity of less than 40 units in the donor's blood, the probability of acquiring hepatitis existed for 1 of 173 recipients of one transfusion; with an SGO-T level of greater than 100 units, the probability of hepatitis was 1 of 47 persons receiving one transfusion. This is a hopeful approach to the problem of screening donors and, if the results are shown to be reproducible, the method should be generally adopted.

In all instances, with the existing difficulties in the recognition of the carrier state, the indications for the administration of blood or blood products should be carefully weighed to avoid aggravating the condition of a sick patient by superimposing another disease.

All equipment which comes in contact with blood or its derivatives should either be discarded or be thoroughly cleaned and then sterilized with heat, by boiling or autoclaving for 30 minutes at 121 F. The use of disposable needles, syringes and infusion equipment is strongly recommended to reduce the chance of contamination.

No person who has a history of jaundice or abnormal results of liver function tests should serve as a blood donor. At best, these measures will not exclude all carriers, but with the addition of SGO-T to the tests, the score may be improved.

It has been shown that the larger the plasma pool, the greater the possibility of its containing virus. Plasma pools, therefore, should be derived from small numbers of donors.

Although the heating of serum albumin at 60 C. for 10 hours has been shown to inactivate virus without untoward effect on the albumin, this method is not applicable to whole blood or its other components. The use of ultraviolet light has proved unreliable as a virucidal agent. The storage of plasma at room temperature for long periods (6 months and over) has yielded promising results, but because of problems inherent in storage may turn out to be impracticable. This method and the addition of beta-propiolactone to plasma, which also seems promising, need further investigation.

Although the value of gamma globulin in the prevention of serum hepatitis is *sub judice,* the available evidence is highly suggestive that 10 ml. at the time of transfusion and 10 ml. a month later may reduce the incidence of subsequent hepatitis with jaundice.

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